hæmoglobin was 60 per cent., and the leucocytes and blood plates were normal in number. His temperature has been mostly subnormal—97° to 98°, but on five different occasions it has risen in the early evening to 101° or slightly over.

After a fortnight's stay in hospital the indigestion, diarrhoea, and bronchitis had all disappeared, and he felt stronger, but the attacks of acute joint pain followed by fresh purpuric eruptions still continued to occur every few days. He was kept on a bland but liberal diet, and gained 9 lbs. in weight during two months, so that his general nutrition has not suffered from his illness.

On March 23rd a more careful examination was made of the blood. With his consent 2 ounces were obtained by venesection and received into a cylindrical glass vessel. The blood clotted in five or six minutes, which is an average time, and next day the serum had separated out normally, leaving a firm clot which showed nothing unusual. Tested also by means of Wright's coagulometer the clotting time was found to be three minutes, which is the normal interval for such small quantities of blood. There was no difficulty in checking the hæmorrhage from the venesection. The red corpuscles equalled 5,200,000 per c.mm., the hæmoglobin 72 per cent., the leucocytes and blood plates were in the usual proportions, and the specific gravity was 1065. The red corpuscles were regular in size and shape and stained normally, but they did not form rouleaux. When a large drop of fresh blood was allowed to fall on a microscope slide it clotted in the same time as a drop of blood from a healthy person, but granules formed in it readily visible to the naked eye, and under the microscope these were seen to be due to the red blood corpuscles having run together into irregular clumps. This was the only peculiarity observed in his blood, and it persisted during the whole time of his stay in hospital. Two other patients in the ward suffering from tubercle of the lungs and pleura with high temperature showed the same peculiarity, but it was not seen in any other cases or in any of the students attending the clinique. I do not know what is the significance of this peculiar agglomeration of the red corpuscles or in what other cases it occurs, and on looking through the literature I can find no account of it given previously. It is probably due to some change in the plasma, as the blood serum of our patient when mixed with a drop of healthy blood caused the same granular appearance.

TREATMENT.

The treatment has consisted in confining the patient to bed for the first few weeks and keeping him on an easily-digested diet, and under this the diarrhoea, gastric dyspepsia, bronchitis, and feeling of weakness speedily disappeared. As regards drugs he got 20 grains of salicin four times daily for twenty-three days, then 1 drachm liquor calcis saccharatus thrice daily for six days, then extractum ergotæ liquidum 20 minims thrice daily for ten days, then oleum terebinthine 10 minims four times daily for twenty-seven days, and finally quinine sulphas 10 grains thrice daily for the last three days. Salicylic compounds are recommended in purpura rheumatica owing to a supposed connection between it and acute rheumatism, but as I shall shortly explain to you, arthritis is a symptom common to many specific affections, such, for instance, as scarlet fever, in which the salicylates have no curative effect. Lime salts are supposed to increase the coagulability of the blood and to lessen any tendency to hæmorrhage, but in this case there was neither a decrease of coagulability nor a hæmorrhagic tendency, so their administration could hardly be expected to do any good. Ergot and turpentine have both a great reputation as hæmostatics in purpuric bleeding. During the three days that quinine has been exhibited one outbreak of purpura has occurred. Arsenic has been advocated in purpura, and lately the intravenous injection of mercuric chloride, but both in the hæmorrhagic form of the disease, and I have had no experience with either in these cases.

I cannot say that any of the remedies given seemed to exert the slightest effect either on the joint pains or on the recurrent purpuric hæmorrhages. Both kept on recurring every few days and only towards the end of his stay in hospital with diminishing severity, a result which is probably to be attributed rather to the natural abatement of the disease than to any specific effect of the remedies employed.

This is a typical case of purpura rheumatica (peliosis rheumatica as described by Schönlein in 1837), the dyspepsia and diarrhoea, the joint pains, the purpuric eruption, the pains in the muscles, the slight albuminuria, the very slight degree of fever, and the general weakness, constituting the usual symptoms. Epistaxis and endocarditis are also not uncommon in the course of the disease, but they have been absent in this patient. It is apt to recur at intervals; each attack may last for a week or two or for several months. The prognosis is favourable, but one should be careful in expressing an opinion as to its probable duration.

With regard to the nature of the disease it is probably a specific infection accompanied by arthritis and purpuric eruptions, but we have absolutely no knowledge as to any specific microbe or the toxins which are responsible for the symptoms. It is to be remembered, however, that arthritis and purpura, either singly or together, are not uncommon accompaniments of various intoxications. Thus we find purpura occurring in pyæmia, small-pox, scarlatina, and other fevers, in pernicious anaemia, leukaemia, sprue, scurvy, in poisoning by potassium iodide, phosphorus, potassium chlorate, snake venom, and in numerous other conditions, while arthritis is a prominent symptom of acute rheumatism, rheumatoid arthritis, gonorrhoeal rheumatism, dengue, etc.

It is readily enough distinguished from acute rheumatism by the comparative mildness of the arthritis, by the absence of serious febrile disturbance, by the absence of acid perspirations, by its chronic course, by the purpura, and by the salicylates having no effect.

Hæmorrhagic purpura is probably a totally different disease, the cause of which is also unknown. In it, however, the bleeding may be very severe, and the prognosis grave. The pains in the joints are absent. Hayem says that the hæmatoblasts are greatly diminished in number, and that although the blood coagulates in the normal time, the clot does not contract, and the serum does not separate from it on standing. If these changes in the blood are invariably present they constitute points of great diagnostic importance.

In scurvy the larger hæmorrhages, the state of the gums, and the dietetic history render the diagnosis easy, and distinguish it from all varieties of purpura. Hæmophilia and leukaemia are scarcely likely to be mistaken for purpura rheumatica, although sometimes they bear a resemblance in symptoms to purpura hæmorrhagica.

THE CROONIAN LECTURES

ON

THE CHEMICAL SIDE OF NERVOUS ACTIVITY.

[ABSTRACT.]

*Delivered at the Royal College of Physicians, London,
June, 1901.*

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LECTURE III.

THE lecturer stated that in his two concluding lectures he proposed to deal with the more strictly pathological side of the subject. Chemical pathology is a comparatively new branch of science, and has a great future before it. He stated that the credit of opening up a new area of research, namely, the application of chemical methods to the investigation of nervous diseases, should be largely given to his colleague, Dr. Mott. The three researches with which he proposed to deal were:

1. The Chemical Pathology of Hyperpyrexia.
2. The Chemical Pathology of General Paralysis of the Insane.
3. The Chemistry of Wallerian Degeneration.

THE CHEMICAL PATHOLOGY OF HYPERPYREXIA.

The experiments on this subject were described in detail, but they may be summed up by saying that they fully confirm the hypothesis that the physico-chemical cause of death

from hyperpyrexia is heat coagulation of cell globulin. When this constituent of cell protoplasm is coagulated, the vitality of protoplasm is destroyed, just as muscle loses its irritability when the corresponding proteid in that tissue is coagulated. The temperature at which such coagulation is most readily produced is 47°C . Such a temperature in animals is almost instantaneously fatal; but 47°C . (117°F .) is unknown in man. Nevertheless, proteids will coagulate at temperatures below their normal coagulating point provided the heating is continued long enough. In the case of cell globulin, coagulation can be produced by a temperature as low as 42°C . (108°F .). This chemical change in the brain substance can be demonstrated by experiments with saline extracts of that tissue, or with the "surviving" brain of animals just killed. They are coincident with the histological (chromatolytic) changes in the nerve cells which can be rendered evident by the use of the methylene blue process. The expression "coagulation necrosis" employed by Marinesco for this appearance is therefore justifiable. Marinesco and others who have employed exclusively histological methods of research have naturally failed to grasp the chemical meaning of their observations, and have consequently missed the connection of the temperature necessary to produce these changes with that of the coagulation temperature of cell globulin. Although the nerve cells are those which lend themselves most readily to the histological part of the research, it is by no means improbable (looking at the wide distribution of cell globulin) that many other cells of the body are affected by high temperatures in a corresponding manner; some varieties of what is called "cloudy swelling" are without doubt instances of coagulation necrosis.

CHEMICAL PATHOLOGY OF GENERAL PARALYSIS OF THE INSANE.

The lecturer stated that his work (in connection with Dr. Mott) on this subject, had been previously published; he therefore would only describe it in general terms. He did so, in order to lead up to the consideration of the third pathological subject he proposed to deal with, and which he reserved for his final lecture.

The cerebro-spinal fluid removed from cases of general paralysis of the insane is much increased in quantity, and takes the place of the atrophied brain material. It produces when injected into the circulation of anæsthetised animals (dogs, cats, rabbits), a fall of arterial blood pressure, with little or no effect on respiration. This pathological fluid is richer in proteid matter than the normal fluid, and among the proteids nucleo-proteid is present. The fall of blood pressure is, however, due not to proteid nor to inorganic constituents, but to an organic substance, which is soluble in alcohol. This substance is precipitable by phospho-tungstic acid, and by chemical methods was identified as choline. The crystals of the platinum double salt, which, when crystallised from 15 per cent. alcohol, are characteristic octahedra, form the most convenient test for the separation and identification of this base.

The nucleo-proteid and choline doubtless originate from the disintegration of the brain tissue, and their presence indicates that possibly some of the symptoms of general paralysis may be due to autointoxication; these substances pass into the blood, for the cerebro-spinal fluid acts as the lymph of the central nervous system. Choline can be detected in the blood removed by venesection from those patients during the convulsive seizures which form a prominent symptom in the disease.

Normal cerebro-spinal fluid does not contain nucleo-proteid and the amount of choline is so small that it cannot be readily identified. Normal cerebro-spinal fluid produces no effect on arterial pressure; neither does the alcoholic extract of normal blood or of ordinary dropsical effusions.

The presence of choline in the pathological cerebro-spinal fluid and blood will not explain all the symptoms of general paralysis; for instance, it will not account for the fits just referred to. Its presence, however, is an indication that an acute disintegration of the cerebral tissues has occurred. If other poisonous substances are also present, they have still to be discovered.

The proof that the toxic material is choline rests not only on chemical tests, but also on the evidence afforded by physiological experiments; the action of the cerebro-spinal substance exactly resembles that of choline. Neurine, an alkaloid closely related to choline, is not present in the fluid; its toxic action is much more powerful, and its effects differ considerably from those of choline.

Physiological Action of Choline.—The doses employed were from 1 to 10 c.cm. of a 0.2 per cent. solution, either of choline or of its hydrochloride. These were injected intravenously in anæsthetised animals. The fall of blood pressure is in some measure due to its action on the heart, but is mainly produced by dilatation of the peripheral vessels, especially in the intestinal area. This was demonstrated by the use of an intestinal oncometer. The limbs and kidneys are somewhat lessened in volume; this appears to be a passive effect, secondary to the fall in general blood pressure. The drug causes a marked contraction of the spleen, followed by an exaggeration of the normal curves, due to the alternate systole and diastole of that organ.

The action on the splanchnic vessels is due to the direct action of the base on the neuro-muscular mechanism of the blood vessels themselves; for after the influence of the central nervous system has been removed by section of the spinal cord or of the splanchnic nerves, choline still causes the typical fall of blood pressure. The action of peripheral ganglia was in other experiments excluded by poisoning the animal previously with nicotine.

Section of the vagi produces no effect on the results of injecting choline. There was no evidence of any direct action of the base on the cerebral vessels. Choline has no effect on respiration.

The effect of choline soon passes off, and the blood pressure returns to its previous level. This is due partly to the great dilution of the substance injected by the whole volume of the blood, and may be partly due to the excretion of the alkaloid, or to its being broken up into simpler substances by metabolic processes. It does not pass as such into the urine.

If the animal has previously received an injection of atropine, the effect produced by choline is a rise of arterial pressure, accompanied by a rise of the lever of the intestinal oncometer. This observation appears to be of some importance, for it shows how the action of one poison may be modified by the presence of another. This has some bearing on general paralysis, for the arterial tension in the early stages of that disease is usually high, not low, as it would be if choline were the only toxic agent at work. After a succession of fits the tension sinks, and this may be explained as a result of choline action.

Physiological Action of Neurine.—The doses employed varied from 1 to 5 c.cm. of a 0.1 per cent. solution. These were injected intravenously. Neurine produces a fall of arterial pressure, followed by a marked rise, and a subsequent fall to the normal level. The effect of neurine on the heart of both frog and mammal is much more marked than is the case with choline; in the case of both choline and neurine, the action on the heart is antagonised by atropine. The slowing and weakening of the heart account for the preliminary fall of blood pressure. The rise of blood pressure which occurs after the fall is due to the constriction of the peripheral vessels, evidence of which was obtained by the use of oncometers for intestine, spleen, and kidney. It produces a marked effect on the respiration. This is first greatly increased, but with each successive dose the effect is less, and ultimately the respiration becomes weaker, and ceases altogether. The animal can still be kept alive by artificial respiration. In large doses neurine acts like curare on the nerve endings of voluntary muscle.

It should be mentioned that in the cases of brain atrophy referred to, the cerebro-spinal fluid was removed as a rule soon after death. Specimens removed during life by lumbar puncture give, however, the same results.

The lecture was illustrated by a number of lantern slides to show the histological changes in nerve cells referred to; and also the graphic records of the experiments on blood pressure, etc., in connection with choline, neurine, and cerebro-spinal fluid.

LECTURE IV.

THE CHEMISTRY OF NERVE DEGENERATION.

THE concluding lecture dealt with the chemistry of Wallerian degeneration, the third of the pathological questions to which the lecturer had alluded at the commencement of his previous lecture.

It has been now shown that in the disease, general paralysis of the insane, the marked degeneration that occurs in the brain is accompanied by the passing of the products of degeneration into the cerebro-spinal fluid. Of these, nucleo-proteid and choline are those which can be most readily detected. Choline can also be found in the blood. On continuing work in this direction, it was found that this is not peculiar to the disease just mentioned, but that in various other degenerative nervous diseases (combined sclerosis, disseminated sclerosis, alcoholic neuritis, and beri-beri) choline can also be detected in the blood. The tests employed to detect choline are mainly two: (1) A chemical test, namely, the obtaining of the characteristic octahedral crystals of the platinum-chloride from the alcoholic extract of the blood; and (2) a physiological test, namely, the lowering of blood pressure (partly cardiac in origin, and partly due to dilatation of peripheral vessels), which a saline solution of the residue of the alcoholic extract produces; this fall is abolished or even replaced by a rise of arterial pressure if the animal has been atropinised. It is possible that such tests may be of diagnostic value in the distinction between organic and so-called functional diseases of the nervous system. The chemical test can frequently be obtained with 10 c.cm. of blood.

A similar condition of the blood was produced artificially in cats by a division of both sciatic nerves, and is most marked in those animals in which the degeneration process is at its height, as tested histologically by the Marchi reaction.

The Marchi reaction is the black staining produced by Marchi's fluid, a mixture of Muller's fluid and osmic acid, after the tissue has been previously hardened in Muller's fluid. Osmic acid by itself stains the medullary sheath of fresh healthy nerve fibres black; but if the healthy nerve fibres have been previously treated with a chromic solution like Muller's fluid, they take on a greenish-grey colour with Marchi's fluid. Neutral fat, on the other hand, such as in ordinary adipose tissue, is stained black by Marchi's fluid under all conditions; and the degenerated fat which appears in Wallerian degeneration resembles the fat of adipose tissue in this respect. The chemical explanation of the Marchi reaction is the replacement of phosphorised by non-phosphorised or neutral fat. When the Marchi reaction disappears in the later stages of degeneration, the non-phosphorised fat has been absorbed. These facts were established by chemical analysis of the nerves.

The axis cylinder participates in the fatty degeneration; and the multiplication of the nuclei of the primitive sheath is first noticed about the eighth day, and is possibly due to the irritation set up by the presence of the products of disintegration.

The main facts regarding the experiments in animals may be summarised as follows:

A series of 18 cats was taken, both sciatic nerves were divided, and the animals were subsequently killed at intervals varying from 1 to 106 days. The nerves remain practically normal as long as they remain irritable; that is, up to three days after the operation. They then show a progressive increase in the percentage of water, and a progressive decrease in the percentage of phosphorus until degeneration is complete. When regeneration occurs the nerves return approximately to their previous chemical condition. The absorption of the fatty products occurs earlier in the peripheral nerves than in the central nervous system.

This confirms previous observations by Mott and Barratt on human spinal cords, in which unilateral degeneration of the pyramidal tract by brain lesions produced an increase of water and a diminution of phosphorus in the degenerated side of the cord, which stained by the Marchi reaction.

The main results of the experiments on animals are given in the following table:

Cats' Sciatic Nerves.

Days After Section.	Water.	Solids.	Percentage of Phosphorus in Solids.	Condition of Blood.	Condition of Nerves.
Normal					
1-3	65.1 64.5	34.9 35.5	1.1 0.9	Minimal traces of choline present	Nerves irritable, and histologically healthy.
4-6	69.3	30.7	0.9	Choline more abundant	Irritability lost; degeneration beginning.
8	68.2	31.8	0.5	Choline abundant	Degeneration well shown by Marchi reaction.
10	70.7	29.3	0.3		
13	71.3	28.7	0.2		Marchi reaction still seen, but absorption of degenerated fat has set in.
25-27	72.1	27.9	Traces	Choline much less	Absorption of fat practically complete.
29	72.5	27.5	0.0		
44	72.6	27.4	0.0	Choline almost disappeared	Return of function; nerves regenerated.
100-106	66.2	33.8	0.9		

Our chemical knowledge of the process of Wallerian degeneration is thus mainly limited to what occurs in lecithin, the main constituent of myelin. This substance is broken up into its constituents, and each of these is in time removed by absorption. The products of disintegration are four in number:

1. Choline. This is removed first, and can be detected for a time in the blood.

2. Phosphoric acid. This disappears next.

3 and 4. Fatty acid and glycerine. These are the elements of a neutral fat, and the fat so formed resembles other neutral fats by giving the black Marchi reaction. In time, however, this is removed also. In the removal of the fat, certain cells, probably the hypertrophied cells of the neurilemma can be seen microscopically to play a phagocytic rôle.

Noll has shown another interesting fact in connection with "disuse atrophy;" that is, the change which occurs in the central end of a divided nerve before regeneration has occurred. Here there is also some diminution in the amount of protogon, though not nearly so great as in the peripheral end of the nerve.

The lecture was illustrated by a number of lantern slides, to show the relationship between the histological and chemical changes which occur in divided nerves.

Other slides were reproductions of the tracings showing the effects upon arterial pressure of the choline separated out from the blood of the cases of nervous disease mentioned, and from the blood of the cats operated on.

These and others will be reproduced, and full details of all the experiments given when the lecturer publishes these lectures in a separate form, which he hopes to be able to do shortly.

TRANSPLANTATION OF URETERS INTO RECTUM BY AN EXTRAPERITONEAL METHOD FOR EXSTROPHY OF BLADDER,

AND A NEW OPERATION FOR PROCIDENTIA RECTI IN THE SAME PATIENT.

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EITHER of the two surgical conditions—ectopia vesicæ and procidencia recti—is serious enough in itself, but the occurrence of both in one subject makes the sufferer's life so unutterably miserable, and renders him so repulsive to his friends, that life without relief is well-nigh intolerable.

B. S. G., aged 2 years 7 months, came under my care at the Victoria Hospital for Sick Children on September 29th, 1896.

History and State on Examination.—His parents were healthy and robust, as were also his four brothers and one sister. At birth the patient was found to present a healthy and well-developed appearance in all respects, except that there was an ectopia vesicæ or exstrophy of the